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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,677	10/01/2001	Samuel J. Davis	REG 670A-US	3022

7590 05/02/2005

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,677	DAVIS ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49,50,59-72 and 77-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49,50,59-72 and 77-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 9, 2004 has been entered.

Claims Status

2. Claims 49, 50, 59-72 and 77-90 are pending in the instant application. Claims 49, 50, 59, 62, 63, 64, 71, 80 and 85 have been amended, claims 42-48, 53, 54, 58 and 73-76 have been canceled and claims 89 and 90 have been added as requested by Applicant in the Paper filed August 9, 2004.

All claims are under examination.

Withdrawn Objections and Rejections

3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Claim Objections

4. Claims 89 and 90 are objected to because of the following informalities: they recite Ang1-FD or Ang2-FD, and FD should be spelled out fibrinogen domain for clarity. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 49, 50, 59-72 and 77-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al., US Patent No. 6,265,564, filing date Oct. 25, 1996, and further in view of Sakano et al., US Patent No. 6,337,387, filing date June 18, 1998,

Claims had previously been rejected as being obvious over Davis et al., Pack et al. and Desnick et al., but are now rejected over Davis et al. and Sakano et al.

Claims 49, 50, 59-72 and 77-90 encompass nucleic acid molecules encoding a fusion polypeptide wherein the fusion polypeptide consisists of a first subunit consisting of at least one copy or more than one copy of the receptor binding domain of angiopoietin-1, the first subunit being fused to the N-terminal end of a multimerizing component, and the multimerizing

component being fused at its C-terminal end to a second subunit comprising at least one copy or more than one copy of the receptor binding domain of angiopoietin-1, nucleic acid molecules encoding a similar fusion polypeptide wherein wherein angiopoietin-1 is replaced by angiopoietin-2, wherein the multimerizing component may be Fc domain of IgG, the encoded fusion proteins, wherein the fusion polypeptide is multimerized, wherein the multimer is a dimer formed by interaction between the multimerizing components of two adjacent fusion polypeptide molecules, wherein the receptor binding domains are fused contiguously, wherein the multimer may be tetrameric with respect to the fibrinogen-like domains, compositions comprising the multimerized fusion polypeptides, expression vectors in which the encoding nucleic acids are operably linked to an expression control sequence, host-vector system for the production of the fusion polypeptide wherein the host may be E. coli, a yeast or mammalian cell, and method of recombinantly producing the fusion polypeptide.

Davis et al. disclose TIE-1 and TIE-2 ligands, which are the same proteins as angiopoietin-1 and angiopoietin-2, respectively, and teach that the two ligands both bind the TIE-2 receptor. TIE-1 ligand is an agonist of the TIE-2 receptor, and TIE-2 ligand is an antagonist of the TIE-2 receptor. Both ligands contain a "coiled coil" domain and a fibrinogen-like domain. Davis et al. constructed fusion proteins comprising domains of the TIE ligands and Fc domain of IgG, and teach that the Fc section of human antibody IgG1 dimerizes upon expression by mammalian cells (column 44, lines 17-34). Davis et al. disclose experiments in which they demonstrate that the "coiled coil" domain functions as a multimerizing component and the fibrinogen-like domain is the receptor binding domain, but that monomeric forms of the fibrinogen-like domain do not bind the receptor unless they are joined to a "coiled coil" domain,

an Fc domain, or myc-tag and "clustered" using anti-myc antibodies. Davis et al. also teach that the TIE ligands can only bind in dimeric, trimeric or higher multimeric forms, and that the dimeric form of the fibrinogen-like domain of either TIE-1 or TIE-2 (fused to Fc) can bind the TIE-2 receptor, whereas monomeric forms cannot (column 18, line 39 to column 19, line 11, column 43, line 40 to column 44, line 60, and Table 1). At column 44, lines 49-60, Davis et al. also states:

> The differences in behavior between the myc-tagged F-domain truncation and the Fc-tagged F-domain truncation described previously suggested that the TIE ligands can only bind in dimeric or higher multimeric forms. Indeed, non-reducing SDS-PAGE showed that the TIE ligands exist naturally in dimeric, trimeric, and multimeric forms. That the FLAG-1C1F and FLAG-2C2F truncations can bind to the TIE-2 receptor without dimerization by a synthetic tag (such as Fc), whereas the F truncations cannot, suggests that the C-region is at least partly responsible for the aggregation of the F-domains.

Davis et al. teach that the ligands could be important therapeutically in methods such as blocking blood vessel growth, promoting neovascularization, promoting the growth or differentiation of a cell expressing the TIE receptor, method of blocking the growth or differentiation of a cell expressing the TIE receptor and a method of attenuating or preventing tumor growth in a human (abstract, column 19, lines 2 to 65). Davis et al. also teach nucleic acids encoding the fusion proteins, compositions comprising the fusion polypeptides, expression vectors in which the encoding nucleic acids are operably linked to an expression control sequence, host-vector system for the production of the fusion polypeptide wherein the host may be *E. coli*, a yeast or mammalian cell, and method of recombinantly producing the fusion polypeptide (abstract, column 3, line 60 to column 4, line 14, column 11, line 10 to column 12, line 65).

Davis et al. does not specifically teach the claimed fusion proteins, consisting of a first subunit consisting of at least one copy or more than one copy of the receptor binding domain, the first subunit being fused to the N-terminal end of a multimerizing component, and the multimerizing component being fused at its C-terminal end to a second subunit comprising at least one copy or more than one copy of the receptor binding domain, wherein the more than one copy of the receptor binding domains are fused contiguously.

Sakano et al. disclose a ligand for Notch, Serrate-1, which is shown to inhibit differentiation and proliferation of undifferentiated blood cells. In Example 10, they demonstrated that the dimeric form of Serrate-1, a fusion protein of Serrate-1 fused to Fc, was more active than the monomeric form (Fig. 3). At column 16, lines 16-52, Sakano et al. state:

> As shown in Example 10, since the suppressive action of human Delta-1 and human Serrate-1 is stronger in the IgG chimera protein having dimer structure, a form of stronger physiological activity is preferably expressed in the form of multimer formation.
>
> Human Delta-1 and human Serrate-1 having multimer structure can be produced by a method of expressing chimera protein with human IgG Fc region as described in the example and expressing the multimer having disulfide bond with hinge region of the antibody, or a method expressing chimera protein, in which antibody recognition region is expressed in the C-terminal or N-terminal, and reacting with the polypeptide containing extracellular part of the thus expressed said human Delta 1 and Human Serrate 1 and the antibody which recognize specifically the antibody recognition region in the C-terminal or N-terminal. In the other methods, a method, in which a fused protein expressed with only the hinge region of the antibody and the dimerized by disulfide bond, can be mentioned. The multimer of human Delta-1 and human Serrate-1 having higher specific activity than the dimer can be obtained. The said multimer is constructed by fused protein which is prepared for expressing the peptide in the C-terminal, N-terminal or other region. The protein is prepared in the form of forming disulfide bond without effecting in any activities of the other human Delta-1 or human Serrate-1. The multimer structure can also be expressed by arranging one or more peptide, which is selected from polypeptides containing amino acids sequence of the sequence listing, SEQ ID NO: 2, 3, 5 or 6, with genetic engineering method in series or in parallel. Other known methods for providing multimer structure having dimer or higher can be applied. Accordingly, the present invention includes any polypeptides containing amino acid sequences described in the sequence listing, SEQ ID NO: 2, 3, 5 or 6 in the form of dimer or higher structure prepared by genetic engineering technique.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to make fusion proteins comprising one or more domains of receptor binding domains of ligands such as angiopoietin-1 or angiopoietin-2, separated by a multimerizing component such as Fc domain of IgG, as taught by Sakano et al., since Sakano et al. teach that multimers having more domains would have greater activitiy, and since Davis et al. teach that the monomer of angiopoietin-1 or angiopoietin-2 can't bind the receptor, dimer can bind but not active the receptor, and that angiopoietin-1 or angiopoietin-2 exist naturally as higher order multimers. One of ordinary skill in the art would be motivated to make such fusion proteins that are active in binding and activating or inhibiting the receptor, since Davis et al. teaches that such modified ligands could be used diagnostically or therapeutically. Alternatively, multimeric fusion proteins can be used in a research setting, in order to determine if such fusion proteins are more potent activators or inhibitors. Since Davis et al. teach that the Fc domain of IgG can multimerize proteins fused to it and that both angiopoietin-1 and angiopoietin-2 can't bind the TIE-2 receptor as monomers, it would also have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use Fc domain of IgG as the multimerizing component, and to make such constructs using the receptor binding domain of angiopoietin-1 and/or angiopoietin-2. It would also have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to produce the fusion proteins in bacterial cells such as *E. coli*, yeast cells, insect, COS or CHO cells, as taught by Davis et al. The skilled artisan would be motivated to make these fusion constructs since these constructs would be useful either diagsnotically, therapeutically or for research purposes, as discussed above, and given the state of the art of molecular biology, such fusions can easily be constructed

and expressed in cells. There would be a reasonable expectation of success, since the methods of making such fusion proteins are well-established.

It is believed that all pertinent arguments have been answered.

Conclusion

6. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (571) 272-0829.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to

the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner